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Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study)

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Introduction

Overactive bladder (OAB) syndrome is characterized by urinary urgency, with or without urgency urinary incontinence, usually accompanied by increased daytime frequency and nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology [1]. Urgency urinary incontinence is present in approximately one-third of cases [2], but is not a prerequisite. However, of all the OAB symptoms, it has the greatest impact on quality of life (QoL) [3, 4], and is associated with significantly lower productivity and higher healthcare resource utilization [5].

Oral pharmacotherapy for OAB comprises antimuscarinics and mirabegron, a β_3-adrenoceptor agonist. Antimuscarinics and β_3-adrenoceptor agonists modulate bladder function through different molecular pathways; nevertheless, efficacy is similar for both drug classes [6]. In clinical practice, antimuscarinics are often initially prescribed; however, increasing the dose may exacerbate antimuscarinic adverse events (AEs) such as dry mouth and constipation, which may result in treatment discontinuation [7-10]. Analyses of medical claims databases indicate that treatment persistence is better with mirabegron vs antimuscarinics [11-13].

A Phase II European dose-finding study (SYMPHONY; NCT01340027) investigating six dose combinations of mirabegron with solifenacin compared with monotherapy with mirabegron, solifenacin, or placebo, reported that combination therapy demonstrated greater efficacy than solifenacin 5 mg alone on change from baseline to end of treatment (EoT) in mean volume voided (MVV)/micturition, frequency of micturitions/24h and urgency episodes. All combinations were well tolerated compared with the monotherapies or placebo [14]. Solifenacin 5 mg combined with mirabegron 25 mg or 50 mg appeared optimal in terms of the benefit/risk profile in this study [15]. In addition, in a trial of patients remaining incontinent after initial treatment with solifenacin for 4 weeks (BESIDE; NCT01908829), solifenacin+mirabegron combination therapy further improved OAB symptoms and was well tolerated compared with solifenacin monotherapy [16]. The current study (SYNERGY) evaluated the potential of solifenacin 5 mg (the recommended daily starting dose and the most widely used dose in clinical practice) in combination with mirabegron 25 mg or 50 mg, to deliver superior efficacy to the individual monotherapies with acceptable tolerability, in the general OAB population with urinary incontinence.

Patients and Methods

Study Design

This was a multinational, multicentre, randomized, double-blind, parallel-group, placebo-

and active-controlled Phase III study (NCT01972841), performed in accordance with the International Conference on Harmonization, Good Clinical Practice and the Declaration of Helsinki. Independent Review Board/Independent Ethics Committee-approved written informed consent was obtained from each patient prior to the study. Patients enrolled at sites in the US also signed a Health Insurance Portability and Accountability Act (HIPAA) authorization form.

Study duration was 18 weeks, comprising a single-blind, 4-week placebo run-in, a 12-week double-blind treatment period, and a 2-week, single-blind, placebo run-out period (Fig. S1). Patients aged ≥18 years who had experienced symptoms of wet OAB (urgency, urinary frequency and incontinence) for ≥3 months were eligible for screening. In patients with mixed stress/urgency incontinence, urgency incontinence had to be the predominant factor as evidenced by diary data and determined by the investigator. Those who recorded on average ≥8 micturitions/24h, ≥1 urgency episode/24h (grade 3 or 4 on the Patient Perception of Intensity of Urgency Scale [PPIUS]/24h [17]), and ≥3 incontinence episodes over the 7-day micturition diary were eligible for randomization to double-blind treatment in a 2:2:1:1:1:1 ratio to daily:

- Solifenacin 5 mg + mirabegron 25 mg (combination 5+25 mg)
- Solifenacin 5 mg + mirabegron 50 mg (combination 5+50 mg)
- Placebo
- Mirabegron 25 mg
- Mirabegron 50 mg
- Solifenacin 5 mg

Exclusion criteria are shown in Table S1.

Efficacy Assessments

Co-primary efficacy variables were change from baseline to end of treatment (EoT) in mean number of incontinence episodes/24h and micturitions/24h, assessed using a 7-day electronic micturition diary. Key secondary efficacy variables were change from baseline to EoT in MVV/micturition and in patient-reported outcomes (PROs). PROs, which will be the subject of a separate manuscript, included change from baseline to EoT in OAB-q Symptom Bother score, Health-related Quality of Life (HRQoL) total score, Patient Perception of Bladder Condition (PPBC), Treatment Satisfaction-Visual Analogue Scale (TS-VAS) and responder analyses.

Other secondary efficacy variables derived from the 7-day micturition diary included change from baseline at weeks 4, 8, 12 and EoT in: mean number of incontinence episodes/24h, micturitions/24h, urgency episodes24h, urgency incontinence episodes/24h and nocturia episodes/24h; the percentage of patients (responders) achieving zero incontinence episodes/24h at EoT in the last 7 days prior to each visit, micturition frequency normalization (<8 episodes/24h) at weeks 4, 8, 12 and EoT; and the number of urgency incontinence episodes and nocturia episodes in the 7-day diary.

Safety Assessments

Safety assessments at each study visit and during the 2-week placebo run-out period included frequency of treatment-emergent adverse events (TEAEs), post-void residual (PVR) volume (assessed by ultrasound), changes from baseline in laboratory parameters and AEs known to be associated with antimuscarinics (including dry mouth, blurred vision, constipation and dyspepsia). Cardiovascular AEs and change from baseline in vital signs, including vital signs in a subset of patients participating in an ambulatory blood pressure monitoring (ABPM) study will be presented in a manuscript focusing on cardiovascular results. Cardiovascular and neoplasm events were adjudicated by independent adjudication committees. AEs were coded using MedDRA v 16.0 and summarized by System Organ Class (SOC) and Preferred Term. TEAEs for urinary retention were also summarized by lower level term and treatment group. TEAEs reported by the investigator as increased PVR or urinary retention were coded to 'PVR increased' or 'urinary retention', respectively. An AE of acute urinary retention was coded to the lower level term of 'acute urinary retention' under the Preferred Term of 'urinary retention'.

Statistical Analysis

The planned sample size was based on the change from baseline in mean micturitions/24h at EoT. Using a 2:1 randomization ratio between combination therapy, and monotherapy and placebo treatment arms, 762 patients in each combination therapy arm and 381 patients in each of the monotherapy and placebo arms provided 90% power to detect a clinically relevant reduction of 0.55 in mean number of micturitions/24h over each monotherapy component at a 2-sided significance level of 0.05. A standard deviation (SD) of 2.7 was assumed, based on a previous study with solifenacin, mirabegron and solifenacin+mirabegron combinations [14]. As combination therapy groups were compared vs both monotherapies, the combined power for both tests was at least 81% (assuming independence and a similar effect size of the combination groups over each monotherapy).

Change from baseline to EoT in mean number of incontinence episodes/24h was analyzed using a separate stratified rank analysis of covariance (ANCOVA) model for each pairwise treatment group difference of interest (e.g., combination treatment vs each monotherapy). The stratified rank ANCOVA methodology was used to calculate *P* values for differences between treatment groups. Point estimates and 95% CIs for differences between treatment groups were estimated in an ANCOVA model with treatment group, sex, age group, previous OAB treatment and geographic region as fixed factors and baseline value as a covariate. Due to the different methodology used to calculate non-parametric *P* values and parametric 95% CIs for differences between treatment groups, there is a chance that a 95% CI includes 0 even though the *P* value is <0.05 or vice versa.

Change from baseline to EoT in mean number of micturitions/24h and key secondary endpoints were analyzed using an ANCOVA model with treatment group, sex, age group, previous OAB treatment and geographic region as fixed factors and baseline value as a covariate.

As there were co-primary and multiple key secondary endpoints and because two combination therapy groups were compared vs their monotherapy components, the type 1 error was controlled at the one-sided 0.025 level by a sequential Bonferroni-based testing procedure following the graphical approach proposed by Bretz et al. [18] (Fig. S2). To reduce complexity, MVV was the only key secondary variable included in the testing procedure. The first statistical comparison was between the combination 5+50 mg and the monotherapies for change from baseline to EoT in incontinence episodes/24h. More detailed information on the statistical analysis is provided in Table S2.

Results

Patient Demographics and Baseline Characteristics

The study was conducted at 435 sites in 42 countries. In general, all treatment arms were similar with respect to demographics and baseline characteristics (Table 1). The majority of patients were female (77%); most patients were white (80%). There were no major differences across treatment groups in baseline values for mean number of incontinence episodes/24h (range 3.2 for the combination 5+50 mg group to 3.6 for the solifenacin 5 mg group) or mean number of micturitions/24h (range 10.7 for the combination groups to 11.2 for the mirabegron 50 mg group). MVV ranged from 152 to 159 mL. Duration of OAB symptoms was similar across treatment groups (overall mean duration 67 months). Most patients (65%) had urgency incontinence only; all other patients had mixed stress/urgency incontinence with urgency as predominant factor. Overall, 46% of patients had received previous OAB medications; 23% of patients had previously received solifenacin and 4% of

patients had previously received mirabegron. Prespecified subgroup analyses showed that patients who were previously treated with OAB medication had more urgency incontinence only (71%) and less mixed stress/urgency incontinence with urgency as predominant factor (29%) than treatment-naïve patients (61% and 39%, respectively). β-blockers were used by 13% of patients prior to the run-in period and by 13% of patients during the double-blind period.

A total of 6991 patients were screened, 6275 patients received placebo run-in medication, 3527 patients were randomized and 3494 (99%) received double-blind treatment. Of these, 3398 (96%) patients were included in the SAF and 3308 (94%) in the FAS. Patients (n=96) from one site were excluded from the SAF and FAS due to protocol non-compliance. The primary reasons for discontinuation were AEs or withdrawal by the patient (Fig. 1).

Efficacy

While the combination 5+50 mg group was superior to solifenacin 5 mg for incontinence, with a mean (SE) adjusted difference of –0.20 (0.12) episodes (95% CI: –0.44, 0.04, *P*=0.033), statistical superiority vs mirabegron 50 mg was not demonstrated; mean (SE) adjusted difference of –0.23 (0.12) episodes (95% CI: –0.47, 0.01, *P*=0.052) (Fig. 2A). Therefore, the primary objective for the combination 5+50 mg therapy was not met. Because the null hypothesis for this test was not rejected, the subsequent hypotheses for mean number of micturitions/24h and MVV/micturition could not be tested. Also, no hypothesis testing could be performed for the combination 5+25 mg group.

Nonetheless, incontinence episodes/24h at EoT decreased vs baseline for all treatment arms. Mean adjusted change from baseline to EoT was greater in the combination groups vs monotherapies and placebo (Fig. 2A). In secondary analyses, all active treatment groups had greater improvements in incontinence episodes/24h vs placebo (nominal *P* values all less than 0.05), with effect sizes for the combination groups (combination 5+25 mg: –0.70 episodes/24h; combination 5+50 mg: –0.65 episodes/24h) that were substantially higher than those obtained with monotherapy (range –0.37 episodes/24h for mirabegron 25 mg to –0.45 episodes/24h for solifenacin 5 mg).

EoT values for micturitions/24h decreased vs baseline for all treatment arms. Adjusted change from baseline to EoT was greater in the combination groups vs monotherapies (combination 5+50 mg, nominal *P* values 0.006 and <0.001 vs solifenacin 5 mg and mirabegron 50 mg, respectively; combination 5+25 mg, nominal *P* values 0.040 and 0.001

vs solifenacin 5 mg and mirabegron 25 mg, respectively) and placebo (nominal *P* values <0.05; Fig. 2B). All active treatment groups had greater improvements in mean numbers of micturitions/24h vs placebo (nominal *P* values <0.05). The effect size was similar across mirabegron monotherapy groups (25 mg: –0.36; 50 mg: –0.39 micturitions/24h) and slightly higher for solifenacin 5 mg (–0.56 micturitions/24h). The effect size in the combination groups (combination 5+25 mg: –0.85; combination 5+50 mg: –0.95 micturitions/24h) suggests a fully additive effect of the combined monotherapies.

Sensitivity Analyses of Co-Primary Efficacy Variables

In sensitivity analyses, change from baseline in the mean number of micturitions/24h and incontinence episodes/24h generally showed consistent results with respect to the effect size; some exceptions can be found Fig. S3.

Key Secondary Efficacy Variables

MVV/micturition at baseline was similar across treatment groups. EoT values increased with respect to baseline for all treatment arms. The mean adjusted change from baseline to EoT was greater in the combination 5+25 mg and 5+50 mg groups (34.84 mL and 39.73 mL, respectively) vs solifenacin 5 mg (30.99 mL), mirabegron 25 mg (13.32 mL), mirabegron 50 mg (21.99 mL), and placebo (8.44 mL) (Fig. 2C).

Improvements in mean adjusted difference in MVV/micturition for the combination 5+50 mg vs solifenacin 5 mg and mirabegron 50 mg were 8.75 mL (nominal *P*=0.005) and 17.74 mL (nominal *P*<0.001), respectively. The combination 5+25 mg group showed an improvement of 21.52 mL (nominal *P*<0.001) vs mirabegron 25 mg and 3.85 mL vs solifenacin 5 mg (nominal *P*>0.05). All active treatment groups except mirabegron 25 mg had improvements in MVV/micturition vs placebo with nominal *P* values less than 0.05. The effect size was largest in the combination 5+50 mg (31.29 mL, nominal *P*<0.001) and smallest in the mirabegron 25 mg group (4.88 mL, nominal *P*=0.178). The effect size in the combination groups was close to additive.

Other Secondary Efficacy Variables

The combination 5+50 mg group was superior to both monotherapy groups at EoT for urgency incontinence episodes, urgency episodes and nocturia; effect sizes appeared to be additive. The combination 5+25 mg group was superior to mirabegron 25 mg for the same variables, except nocturia. In responder analyses at EoT, odds ratios in favour of both combinations vs the monotherapy components were shown for the proportion of patients

with zero incontinence episodes (Table 2) and those achieving micturition frequency normalization (Table 3).

For almost all parameters, differences were significant for combination therapy at week 4, and thereafter remained fairly constant vs monotherapy and placebo. All active treatment groups had nominal *P* values <0.05 compared with placebo at all timepoints. More detailed data are shown in Table S3/Fig. S4.

A substantially greater effect of both combinations was observed in the prespecified analysis of patients who received previous OAB treatment compared with treatment-naïve patients (Fig. 3/Table S4). .

Predefined subgroup analysis of mean number of incontinence episodes/24 h showed that patients who received previous OAB treatment had a considerably larger effect size on combination treatment vs monotherapy than treatment-naïve patients except for the comparison of combination 5+25 mg vs mirabegron. In the subgroup of previously treated patients the 95% CIs for the differences of combination vs both monotherapy components excluded zero, except for the comparison of combination 5+25 mg vs mirabegron. Analysis of mean number of micturitions/24 h showed that patients who received previous OAB treatment had a more than twice as high effect size of combination treatment vs monotherapy than treatment-naïve patients. In previously treated patients the 95% CIs for the differences of combination vs both monotherapy components excluded zero, except for the comparison of combination 5+25 mg vs solifenacin (-0.81, 0.00).

An analysis of MVV/micturition showed that patients who received previous OAB treatment had a much larger effect size of combination treatment vs monotherapy than treatment-naïve patients, especially for the comparison with solifenacin (17.13 and 7.46 mL for the 5+50 mg and 5+25 mg combination groups, respectively, for previously treated patients; 1.48 and 0.59 mL for the 5+50 mg and 5+25 mg combination groups, respectively, for treatment-naïve patients). In previously treated patients, the 95% CIs for the differences of combination vs both monotherapy components excluded zero, except for the comparison of combination 5+25 mg vs solifenacin (-1.50, 16.42 mL).

Analysis of mean number of urgency incontinence episodes/24 h showed that patients who received previous OAB treatment had a much larger effect size of combination treatment compared to monotherapy than treatment-naïve patients, especially for the comparison with solifenacin (-0.43 and -0.53 episodes for the 5+50 mg and 5+25 mg

combination groups, respectively, for previously treated patients; -0.06 and 0.02 episodes for the 5+50 mg and 5+25 mg combination groups, respectively, for treatment-naïve patients). Analysis of mean number of urgency episodes (grade 3 or 4)/24 h showed that patients who received previous OAB treatment, prior to entering the study, had a considerably larger effect size of combination treatment vs monotherapy than treatment-naïve patients. In previously treated patients, the 95% CIs for the differences of combination vs both monotherapy components excluded zero for both urgency incontinence episodes and urgency episodes.

Although differences were small, there seemed to be a trend towards slightly higher effect sizes for endpoints related to incontinence and urgency (mean number of incontinence episodes, mean number of urgency incontinence episodes and mean number of urgency episodes) for patients with urgency incontinence at screening compared to patients with mixed stress/urgency incontinence with urgency as predominant factor.

PRO data will be presented elsewhere.

Safety

Overall, 36% (1235/3398) of patients experienced ≥1 TEAE. A slightly increased frequency of TEAEs was observed in the combination groups vs monotherapies and placebo (Table 4). Incidence of TEAEs was lowest in the mirabegron 25 mg group (32%) and highest in the combination 5+25 mg group (40%). The frequency of treatment-related TEAEs (as assessed by the investigator) was lowest in the mirabegron 25 mg group and highest in the combination 5+25 mg group. The majority of TEAEs in all treatment groups were mild or moderate in severity. There were no meaningful differences between treatment groups in the incidence of TEAEs that led to discontinuation.

Frequency of UTIs was slightly higher in the combination 5+25 mg group compared with other treatment groups, in which the frequency was similar to placebo (Table 4). Events indicative of urinary retention were reported slightly more frequently in the combination groups compared with monotherapy and placebo. Four of these required catheterization, two in the combination 5+25 mg and two in the combination 5+50 mg group. Consistent with these findings, PVR volume was slightly increased in the combination groups compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups (Fig. 4). More patients in the combination groups experienced a shift towards higher PVR categories. There were no notable differences between sexes. The frequency of hypersensitivity reactions was similar between groups, and only in the combination 5+25 mg group was it

slightly higher than placebo and monotherapies. No increased risk of somnolence was identified with combination or monotherapy treatment compared with placebo. Slightly higher frequencies were observed for dry mouth, constipation, and dyspepsia in the combination groups compared with each monotherapy group (Table 4).

Detailed data on vital signs and cardiovascular AEs results will be presented elsewhere. However, in brief, no relevant differences were observed between active treatment groups and placebo or between combination therapy and monotherapy in site-based systolic blood pressure, diastolic blood pressure and pulse rate. No relevant differences appeared to be present between patients using β-blockers vs patients not on β-blockers (data not shown). There were no concerns for ECGs and laboratory data, including QTcF interval and liver function tests.

Discussion

In the largest OAB study to date, combination therapy with solifenacin 5 mg+mirabegron 25 mg and solifenacin 5 mg+mirabegron 50 mg provided improvements in efficacy compared with the respective monotherapies, with effect sizes generally consistent with an additive effect. Most effects of combination therapy vs monotherapy were observable by week 4 and had an additive effect for many parameters. The clinical relevance of the improvements seen with combination therapy for several objective OAB outcome measures was also supported by the improvements of combination vs monotherapy in the responder analyses. The odds of achieving zero incontinence was 31%–50% higher in the combination groups than in the respective monotherapy groups and the *P* values for these odds ratios were statistically significant.

Although the combination 5+50 mg group did not achieve a statistically significant effect vs mirabegron 50 mg in the primary analysis of one of the co-primary endpoints (change from baseline in mean number of incontinence episodes/24h), differences between combination 5+50 mg and both solifenacin 5 mg and mirabegron 50 mg showed nominal *P* values <0.05 when expressed as change from baseline in number of episodes reported in the 7-day diary. Also, improvements in efficacy of combination therapy were seen vs monotherapy for most of the other variables including the co-primary endpoint of mean number of micturitions and the key secondary variable of MVV (except for the combination 5+25 mg vs solifenacin 5 mg). The effect sizes of combination treatment vs placebo in general were similar to the sum of the effect sizes observed in the monotherapy groups vs placebo, indicating the additive effect of combination therapy on many parameters.

Combination 5+50 mg appeared superior to both monotherapies at EoT and most other timepoints for urgency incontinence episodes and urgency episodes. Combination 5+25 mg appeared superior to mirabegron 25 mg for the same variables. The improvement of combination 5+50 mg over monotherapy for nocturia is notable, as improvements for nocturia are uncommon. The effect size of –0.17 vs monotherapy, however, is small and may not be clinically relevant.

Consistent with previous clinical studies, the proportion of women in SYNERGY was higher than men (ratio 3:1). Randomized patients in SYNERGY had an average of just over three incontinence episodes/24h, comparable with just under three incontinence episodes/24h for the incontinent patients in the mirabegron monotherapy studies [19]. A total of 46% of patients had previously received OAB medication, compared with prior Phase III studies with mirabegron monotherapy, in which 50%–60% of patients had previously received OAB medication [19]. As previously noted, there was a larger effect size in patients who had received prior OAB treatment vs treatment-naïve patients, with nominal 95% CIs excluding zero for combinations vs monotherapies for the primary and key secondary endpoints. All patients in the BESIDE study had received previous anticholinergic treatment for OAB as part of the 4-week solifenacin run-in period [16].

Solifenacin at a dose of 10 mg was not included in SYNERGY. The Phase II dose-finding study (SYMPHONY) observed that the efficacy of the 10+25 mg and 10+50 mg combinations was only marginally increased above the efficacy of the 5+50 mg combination, however this was at the expense of an important increase in antimuscarinic side effects in the 10 mg solifenacin combination groups [14]. Therefore it was judged that the benefit/risk of 10 mg combinations was unfavourable and these combinations were not taken to the Phase III studies, of which SYNERGY is the second.

Only OAB patients with incontinence (wet OAB) were enrolled in SYNERGY, as it is expected that combination therapy in clinical practice will be used mostly in highly symptomatic patients. Nevertheless, many patients do not experience incontinence. Indeed, prior Phase III studies with mirabegron monotherapy included the general OAB population, of which approximately two-thirds of patients are not incontinent [2]. In BESIDE, patients were those remaining incontinent after 4 weeks' treatment with solifenacin 5 mg and who then received additional mirabegron. In support of the efficacy of combination therapy demonstrated in SYNERGY, results from BESIDE demonstrated with similar effect sizes that combination therapy with solifenacin and mirabegron for 12 weeks statistically significantly

reduced both mean daily urgency urinary incontinence episodes and micturition frequency in patients who remained incontinent after treatment with solifenacin 5 mg [16].

Differences between patient recruitment and study design in SYNERGY and BESIDE may partially explain the differences in the primary outcomes between the two studies, and may be clinically relevant in considering how to select patients for combination therapy. It is possible that incomplete responders may require more treatment than treatment-naïve patients and that combination treatment may therefore be more effective than monotherapy in this patient subset. Indeed, at baseline, patients who were previously treated with OAB medication had more urgency incontinence only and less mixed stress/urgency incontinence with urgency as predominant factor than treatment-naïve patients.

It should be noted that for all OAB compounds the US Food and Drug Administration (FDA) historically required all urinary incontinence episodes as the primary outcome. The number of urgency urinary incontinence episodes in SYNERGY was very similar to the total number of urinary incontinence episodes, signalling that the vast majority of episodes were urgency; therefore this element does not materially affect the interpretation of the study. For unknown reasons, the effect only for incontinence does not seem to be fully additive. A possible mechanism could be that in most, if not all patients with incontinence, some degree of decreased urinary sphincter function must be present. This factor is not amenable to drug effects, which could perhaps explain the presence of a ceiling effect on incontinence.

In SYNERGY, combination therapy demonstrated a similar safety profile to that expected for the monotherapy components [19, 20], with no new safety findings. A similar proportion of patients discontinued from all groups and the incidence of TEAEs with the combination groups (37%–40%) was similar to that in the BESIDE study (36%) [16]. Regarding TEAEs of special interest, hypersensitivity, glaucoma, somnolence and blurred vision were reported at a similar frequency in the combination groups in SYNERGY vs monotherapy groups or placebo, while there was a slightly higher frequency with UTI in the combination 5+25 mg group vs other groups. All events that could signify a potential risk for urinary retention were captured in this study. Events indicative of urinary retention were reported slightly more frequently in combination groups vs monotherapy and placebo; however most did not require catheterization. Consistent with these findings, PVR was slightly increased in the combination groups vs solifenacin 5 mg and mirabegron monotherapy groups. Dry mouth, constipation, and dyspepsia were also reported at a slightly higher frequency in combination groups vs monotherapy groups and placebo. However,

compared with previous solifenacin 5 mg monotherapy studies, where frequencies of dry mouth, constipation and dyspepsia were around 10%, 5%, and 1% [20], the frequencies of common antimuscarinic side effects were lower in SYNERGY. Since exposures in combination groups were very similar to the monotherapies (data not shown), this increase may not be the result of a drug interaction between mirabegron and solifenacin. Of note, a previous study did appear to suggest the possibility of a drug–drug interaction between mirabegron and solifenacin at high doses [21].

In conclusion, in this study of wet OAB patients, who had previously been exposed to anticholinergic therapy and those who were treatment naïve, combination therapy with solifenacin 5 mg+mirabegron 25 mg and solifenacin 5 mg+mirabegron 50 mg provided improvements in efficacy compared with the respective monotherapies, with effect sizes generally consistent with an additive effect. Although the primary objective was not met – by a small margin – it approached statistical significance for one of the coprimary endpoints (incontinence episodes/24h, P=0.052) and the nominal P values for the other coprimary endpoint (micturitions/24h) were <0.05. In general, the effect size with combination 5+50 mg was larger and more pronounced than with combination 5+25 mg with no obvious differences in safety profile. The improvements seen with combination therapy compared with monotherapy translated into significant improvements in responder rates, supporting the clinical relevance of the effect. Solifenacin+mirabegron combination therapy once daily for 12 weeks had an acceptable safety profile without new safety concerns compared with its monotherapy components and was well tolerated, similar to the monotherapies. It should be noted that the population for the SYNERGY study was large and adequately powered, and was also clinically relevant (comprising only wet patients; a more severe group), but was otherwise very comparable with populations of previous mirabegron monotherapy studies. In addition, the monotherapies performed as expected, and the results of multiple outcome parameters (both subjective and objective) all indicated improvements with combination therapy compared with monotherapy. The most relevant OAB symptom — urgency and incontinence episodes — were improved in the combination vs monotherapy groups.

Conflict of interest

S.H. receives grants and personal fees from Astellas and Allergan; and personal fees from Pfizer and Merus. C.R.C. is a Consultant, Researcher and Speaker for Astellas, Allergan, Medtronic and Recordati; a Consultant and Speaker for Lilly; a Researcher and Speaker for Ono and Pfizer; and a Speaker for Ranbaxy. P.A. is a Consultant for Astellas, Ipsen and Ferring, and a Speaker for Astellas and Pfizer. S.A. is a Consultant for Astellas,

Allergan, Medtronic, Gebro and AMS, a speaker for Astellas, Pfizer, Allergan, Medtronic, Gebro and AMS, a Researcher for Astellas, and has received a research grant from Pfizer. D.M. is a Consultant, Researcher and Speaker for Astellas. K-S.L. is a researcher for Astellas. D.R is a consultant for Astellas, Pfizer, Allergan and Ferring and a speaker for Astellas, Pfizer, Allergan.

A.R., M.S., A.P, and R.v.M. are full-time employees of Astellas Pharma Europe BV.

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Table and Figure legends

Table 1 Patient demographic and other baseline characteristics (Safety Analysis Set).
BMI = body mass index; M = mirabegron; S = solifenacin; SD = standard deviation; UI = urgency incontinence.
* n = 422; † n = 3397.

Table 2 Responders for zero incontinence episodes/24h at end of treatment using the last 3 diary days.
CI = confidence interval; M = mirabegron; S = solifenacin.
*P<0.05.
Odds ratio and P values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 years), previous OAB medication (yes, no) and geographic region as factors and baseline mean number of incontinence episodes per 24h during the last 3 days as a covariate. The two-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the same logistic regression model.

Table 3 Responders for micturition frequency normalization at end of treatment.
CI = confidence interval; M = mirabegron; S = solifenacin.
*P<0.05.

Table 4 Overview of treatment-emergent adverse events (Safety Analysis Set).

CI = confidence interval; M = mirabegron; S = solifenacin; TEAE = treatment-emergent adverse event.

* Based on a sponsor-defined list of Preferred Terms or Lower Level Terms (urinary retention only).

† Based on Lower Level Terms.

$ Based on a standardized MedDRA query.

Fig. 1 Patient disposition.

AE = adverse event

* Excludes 1 patient who entered the placebo run-in period but did not take placebo run-in medication, and did not have end of run-in page provided but was randomized.

†Excludes 4 patients who did not have end of run-in page provided.

‡ Includes 1 patient who entered the placebo run-in period but did not take placebo run-in medication, and did not have end of run-in page provided but was randomized.

§ Patients from one site were excluded from the SAF and FAS due to protocol non-compliance.

¶ Randomized/registered but never received/dispensed study drug.

Fig. 2 Adjusted change from baseline to end of treatment in (A) mean number of incontinence episodes/24h, (B) mean number of micturitions/24h, and (C) mean volume voided/micturition.

M = mirabegron; S = solifenacin.

Fig. 3 Forest plot for treatment difference and 95% CI of adjusted change from baseline in (A) mean number of incontinence episodes per 24h at EoT by previous medication for OAB (yes, no) and (B) micturitions/24h.

M = mirabegron; S = solifenacin.

Fig. 4 Change in post-void residual volume from baseline to end of treatment.

Table S1 Exclusion criteria.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; OAB = overactive bladder; PVR = post-void residual; ULN = upper limit of normal; UTI = urinary tract infection.

Note: During the study it was considered that overall exclusion of β-blockers was overly restrictive; therefore the protocol was amended to allow all β-blockers.

Table S2 Statistical analysis.

Table S3 Other secondary efficacy variables.

Table S4 Subgroup analyses by use of previous OAB medication.

Fig. S1 Study design.

Fig. S2 Testing procedure for the coprimary and key secondary variables based on the micturition diary.

Fig. S3 Forest plots for treatment difference and 95% confidence intervals of adjusted change from baseline to end of treatment in (A) mean number of incontinence episodes/24h and (B) micturitions/24h.
ANCOVA = analysis of covariance; FAS = full analysis set; LOCF = last observation carried forward; M = mirabegron; PPS = per protocol set; S = solifenacin.

Fig. S4 Adjusted change from baseline in (A) mean number of incontinence episodes/24h and (B) micturitions/24h.
M = mirabegron; S = solifenacin.

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Table 1 Patient demographic and other baseline characteristics (Safety Analysis Set).

	Treatment group						Total (*n* = 3398)
	Placebo (*n* = 429)	**M 25 mg (*n* = 423)**	**M 50 mg (*n* = 422)**	**S 5 mg (*n* = 423)**	**S + M 25 mg (*n* = 853)**	**S + M 50 mg (*n* = 848)**	
Sex, *n* (%)							
Male	102 (23.8)	96 (22.7)	99 (23.5)	92 (21.7)	197 (23.1)	197 (23.2)	783 (23.0)
Female	327 (76.2)	327 (77.3)	323 (76.5)	331 (78.3)	656 (76.9)	651 (76.8)	2615 (77.0)
Age, years							
Mean, SD	57.9 (13.0)	56.9 (13.6)	56.7 (13.3)	58.2 (12.8)	57.1 (13.9)	57.6 (13.4)	57.4 (13.4)
Age group, *n* (%)							
≥65 yrs, *n* (%)	146 (34.0)	139 (32.9)	131 (31.0)	138 (32.6)	283 (33.2)	285 (33.6)	1122 (33.0)
≥75 yrs, *n* (%)	38 (8.9)	32 (7.6)	32 (7.6)	35 (8.3)	70 (8.2)	70 (8.3)	277 (8.2)
Race, *n* (%)							
White	346 (80.7)	331 (78.3)	336 (79.6)	335 (79.2)	678 (79.5)	680 (80.2)	2706 (79.6)
Black/African American	14 (3.3)	17 (4.0)	8 (1.9)	13 (3.1)	34 (4.0)	28 (3.3)	114 (3.4)
Asian	60 (14.0)	69 (16.3)	68 (16.1)	66 (15.6)	123 (14.4)	123 (14.5)	509 (15.0)
Other	5 (1.2)	4 (0.9)	6 (1.4)	6 (1.4)	15 (1.8)	12 (1.4)	48 (1.4)
Unknown	4 (0.9)	2 (0.5)	4 (0.9)	3 (0.7)	3 (0.4)	5 (0.6)	21 (0.6)
BMI, kg/m^2 (SD)	28.72 (6.07)	28.19 (6.76)	28.33 (6.03)	28.46 (5.90)*	28.59 (5.86)	28.60 (5.88)	28.51 (6.03)†
Type of OAB at screening, *n* (%)							
UI only	285 (66.4)	267 (63.1)	268 (63.5)	275 (65.0)	561 (65.8)	567 (66.9)	2223 (65.4)
Mixed stress/UI with urgency predominant	144 (33.6)	156 (36.9)	154 (36.5)	148 (35.0)	292 (34.2)	281 (33.1)	1175 (34.6)

Duration of wet OAB symptoms (months)							
Mean (SD)	67.52 (76.02)	69.27 (88.94)	66.78 (80.67)	66.75 (88.76)	68.16 (87.48)	64.34 (81.17)	66.92 (84.03)
Previous OAB medication, *n* (%)							
Yes	205 (47.8)	196 (46.3)	195 (46.2)	204 (48.2)	389 (45.6)	388 (45.8)	1577 (46.4)
Previous treatment with solifenacin, *n* (%)							
Yes	83 (19.3)	92 (21.7)	96 (22.7)	97 (22.9)	198 (23.2)	201 (23.7)	767 (22.6)
Previous treatment with mirabegron, *n* (%)							
Yes	19 (4.4)	18 (4.3)	19 (4.5)	18 (4.3)	27 (3.2)	34 (4.0)	135 (4.0)
7-day micturition diary baseline characteristics (FAS)							
	(*n* = 418)	**(*n* = 410)**	**(*n* = 411)**	**(*n* = 415)**	**(*n* = 827)**	**(*n* = 827)**	**(*n* = 3308)**
Number of incontinence episodes/24h, mean (SD)	3.41 (3.37)	3.42 (3.40)	3.18 (3.47)	3.58 (3.51)	3.22 (3.17)	3.16 (3.08)	3.29 (3.29)
Number of micturitions/24h, mean (SD)	10.97 (2.86)	10.81 (2.63)	11.19 (3.27)	10.76 (2.47)	10.73 (2.88)	10.74 (2.36)	10.84 (2.73)
	(*n* = 414)	**(*n* = 407)**	**(*n* = 409)**	**(*n* = 413)**	**(*n* = 823)**	**(*n* = 824)**	**(*n* = 3290)**
Mean volume voided in mL, mean (SD)	157.94 (58.78)	152.46 (60.96)	155.31 (60.78)	151.94 (59.29)	159.32 (58.29)	153.57 (59.67)	155.43 (59.49)
	(*n* = 415)	**(*n* = 407)**	**(*n* = 405)**	**(*n* = 414)**	**(*n* = 823)**	**(*n* = 822)**	**(*n* = 3286)**
Number of urgency incontinence	3.14 (3.23)	3.00 (3.09)	2.89 (3.31)	3.23 (3.34)	2.85 (2.81)	2.80 (2.64)	2.94 (3.00)

episodes/24h, mean (SD)							
	(*n* = 417)	**(*n* = 409)**	**(*n* = 411)**	**(*n* = 415)**	**(*n* = 827)**	**(*n* = 826)**	**(*n* = 3305)**
Number of urgency (Grade 3 or 4) episodes/24h, mean (SD)	6.52 (4.05)	6.22 (3.89)	6.46 (4.88)	6.48 (3.88)	6.22 (3.70)	6.22 (3.56)	6.32 (3.92)
	(*n* = 368)	**(*n* = 344)**	**(*n* = 356)**	**(*n* = 352)**	**(*n* = 710)**	**(*n* = 704)**	**(*n* = 2834)**
Number of nocturia episodes/24h, mean (SD)	1.57 (1.06)	1.53 (1.02)	1.59 (1.09)	1.59 (0.96)	1.56 (1.07)	1.52 (0.97)	1.56 (1.03)

BMI = body mass index; M = mirabegron; S = solifenacin; SD = standard deviation; UI = urgency incontinence.

* *n* = 422; † *n* = 3397.

Table 2 Responders for zero incontinence episodes/24h at end of treatment using the last 3 diary days.

	Treatment group					
	Placebo (*n* = 412)	**M 25 mg (*n* = 409)**	**M 50 mg (*n* = 406)**	**S 5 mg (*n* = 413)**	**S + M 25 mg (*n* = 823)**	**S + M 50 mg (*n* = 816)**
Responders (%)	155 (37.6)	166 (40.6)	188 (46.3)	177 (42.9)	417 (50.7)	426 (52.2)
Difference vs S, %	NA				7.8	9.3
95% CI (%)					(1.9, 13.7)	(3.5, 15.2)
Odds ratio vs S	NA				1.31	1.40
95% CI (%)					(1.02, 1.69)	(1.09, 1.81)
P value					0.035*	0.009*
Difference vs M, %	NA				10.1	5.9
95% CI (%)					(4.2, 15.9)	(0.0, 11.8)
Odds ratio vs M	NA				1.50	1.34
95% CI (%)					(1.16, 1.93)	(1.04, 1.73)
P value					0.002*	0.023*
Difference vs placebo, %	NA	3.0	8.7	5.2	13.0	14.6
95% CI (%)		(–3.7, 9.6)	(1.9, 15.4)	(–1.4, 11.9)	(7.3, 18.8)	(8.8, 20.4)
Odds ratio vs placebo	NA	1.17	1.40	1.34	1.75	1.87
95% CI (%)		(0.87, 1.57)	(1.04, 1.87)	(0.99, 1.79)	(1.36, 2.26)	(1.45, 2.42)
P value		0.300	0.027*	0.055	<0.001*	<0.001*

CI = confidence interval; M = mirabegron; S = solifenacin.

*$P<0.05$.

Odds ratio and *P* values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 years), previous OAB medication (yes, no) and geographic region as factors and baseline mean number of incontinence episodes per 24h during the last 3 days as a covariate. The two-sided *P* value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the same logistic regression model.

Table 3 Responders for micturition frequency normalization at end of treatment.

	Treatment group					
	Placebo (*n* = 412)	**M 25 mg (*n* = 409)**	**M 50 mg (*n* = 406)**	**S 5 mg (*n* = 413)**	**S + M 25 mg (*n* = 823)**	**S + M 50 mg (*n* = 816)**
Responders (%)	128 (31.1)	172 (42.1)	163 (40.1)	186 (45.0)	422 (51.3)	429 (52.6)
Difference vs S, %	NA				6.2	7.5
95% CI (%)					(0.4, 12.1)	(1.6, 13.4)
Odds ratio vs S	NA				1.30	1.43
95% CI (%)					(1.01, 1.67)	(1.11, 1.84)
P value					0.044*	0.006*
Difference vs M, %	NA				9.2	12.4
95% CI (%)					(3.3, 15.1)	(6.6, 18.3)
Odds ratio vs M	NA				1.47	1.60
95% CI (%)					(1.13, 1.90)	(1.23, 2.08)
P value					0.004*	<0.001*
Difference vs placebo, %	NA	11.0	9.1	14.0	20.2	21.5
95% CI (%)		(4.4, 17.5)	(2.5, 15.6)	(7.4, 20.5)	(14.6, 25.8)	(15.9, 27.1)
Odds ratio vs placebo	NA	1.66	1.67	1.87	2.43	2.67
95% CI (%)		(1.22, 2.25)	(1.23, 2.27)	(1.38, 2.54)	(1.86, 3.18)	(2.04, 3.49)
P value		0.001*	0.001*	< 0.001*	< 0.001*	< 0.001*

CI = confidence interval; M = mirabegron; S = solifenacin.

*$P<0.05$.

Odds ratio and *P* values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 years), previous OAB medication (yes, no) and geographic region as factors and baseline mean number of micturitions per 24h during the last 3 days as a covariate. The two-sided *P* value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the same logistic regression model.

Table 4 Overview of treatment-emergent adverse events (Safety Analysis Set).

	Treatment group					
***n* (%)**	**Placebo (*n* = 429)**	**M 25 mg (*n* = 423)**	**M 50 mg (*n* = 422)**	**S 5 mg (*n* = 423)**	**S + M 25 mg (*n* = 853)**	**S + M 50 mg (*n* = 848)**
TEAEs	145 (33.8)	135 (31.9)	147 (34.8)	149 (35.2)	345 (40.4)	314 (37.0)
Drug-related TEAEs	45 (10.5)	37 (8.7)	52 (12.3)	63 (14.9)	157 (18.4)	150 (17.7)
Serious TEAEs	8 (1.9)	6 (1.4)	5 (1.2)	3 (0.7)	12 (1.4)	19 (2.2)
Drug-related serious TEAEs	0	1 (0.2)	1 (0.2)	0	2 (0.2)	3 (0.4)
TEAEs leading to permanent discontinuation of study drug	9 (2.1)	7 (1.7)	10 (2.4)	7 (1.7)	20 (2.3)	22 (2.6)
Drug-related TEAEs leading to permanent discontinuation of study drug	7 (1.6)	4 (0.9)	6 (1.4)	5 (1.2)	17 (2.0)	19 (2.2)
Urinary tract infection, n (%)*	21 (4.9)	18 (4.3)	16 (3.8)	21 (5.0)	60 (7.0)	44 (5.2)
95% CI	(2.9, 6.9)	(2.3, 6.2)	(2.0, 5.6)	(2.9, 7.0)	(5.3, 8.8)	(3.7, 6.7)
Urinary retention n (%)*	0	0	0	3 (0.7)	8 (0.9)	10 (1.2)
95% CI				(0.0, 1.5)	(0.3, 1.6)	(0.5, 1.9)
Urinary retention, n (%)†	0	0	0	1 (0.2)	4 (0.5)	5 (0.6)
95% CI				(0.0, 0.7)	(0.0. 0.9)	(0.1, 1.1)
Acute urinary retention, n (%)†	0	0	0	0	0	1 (0.1)
95% CI						(0.0, 0.3)
Increased residual urine volume, n (%)†	0	0	0	0	3 (0.4)	3 (0.4)
95% CI					(0.0, 0.7)	(0.0, 0.8)

Residual urine[†]	0	0	0	0	1 (0.1)	0
95% CI					(0.0, 0.3)	
Incomplete bladder emptying[†]	0	0	0	1 (0.2)	1 (0.1)	0
95% CI				(0.0, 0.7)	(0.0, 0.3)	0
Hypersensitivity reactions n (%)[$]	4 (0.9)	4 (0.9)	4 (0.9)	3 (0.7)	9 (1.1)	4 (0.5)
95% CI	(0.0, 1.8)	(0.0, 1.9)	(0.0, 1.9)	(0.0, 1.5)	(0.4, 1.7)	(0.0, 0.9)
Glaucoma n (%)[$]	0	1 (0.2)	0	0	1 (0.1)	1 (0.1)
95% CI		(0.0, 0.7)			(0.0, 0.3)	(0.0, 0.3)
Somnolence n (%)*	11 (2.6)	11 (2.6)	15 (3.6)	12 (2.8)	29 (3.4)	13 (1.5)
95% CI	(1.1, 4.1)	(1.1, 4.1)	(1.8, 5.3)	(1.3, 4.4)	(2.2, 4.6)	(0.7, 2.4)
Common antimuscarinic TEAEs*						
Dry mouth*	8 (1.9)	17 (4.0)	14 (3.3)	25 (5.9)	74 (8.7)	61 (7.2)
Blurred vision*	3 (0.7)	1 (0.2)	0	2 (0.5)	5 (0.6)	6 (0.7)
Constipation*	6 (1.4)	6 (1.4)	11 (2.6)	6 (1.4)	38 (4.5)	31 (3.7)
Dyspepsia*	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)	10 (1.2)	16 (1.9)

CI = confidence interval; M = mirabegron; S = solifenacin; TEAE = treatment-emergent adverse event.

* Based on a sponsor-defined list of Preferred Terms or Lower Level Terms (urinary retention only).

[†] Based on Lower Level Terms.

[$] Based on a standardized MedDRA query.

Figure 1

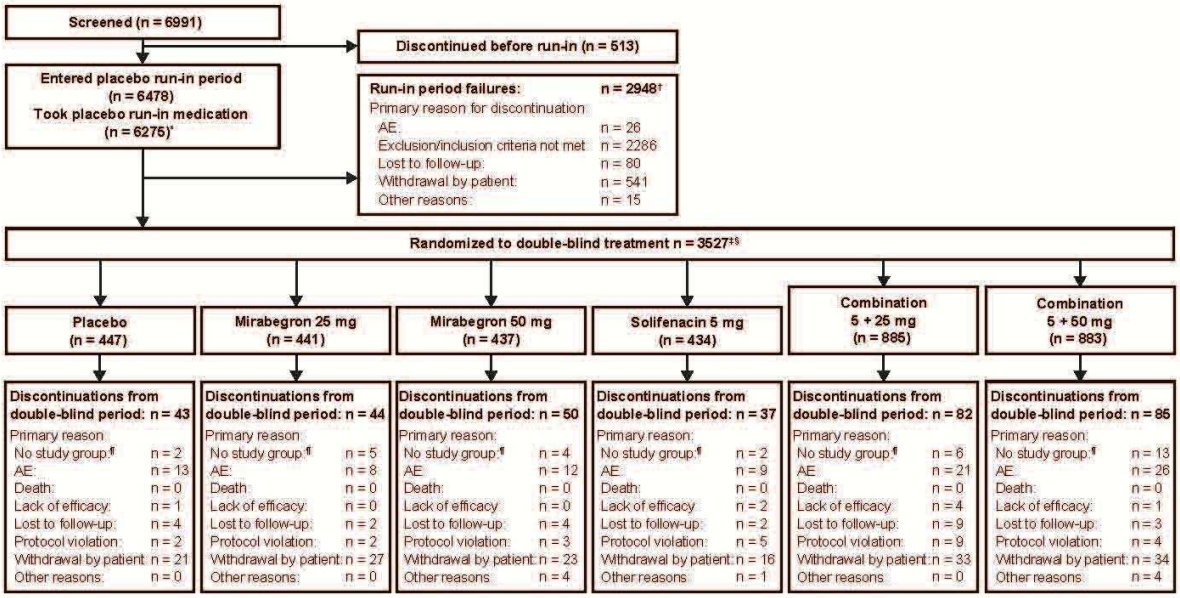


Figure 2A

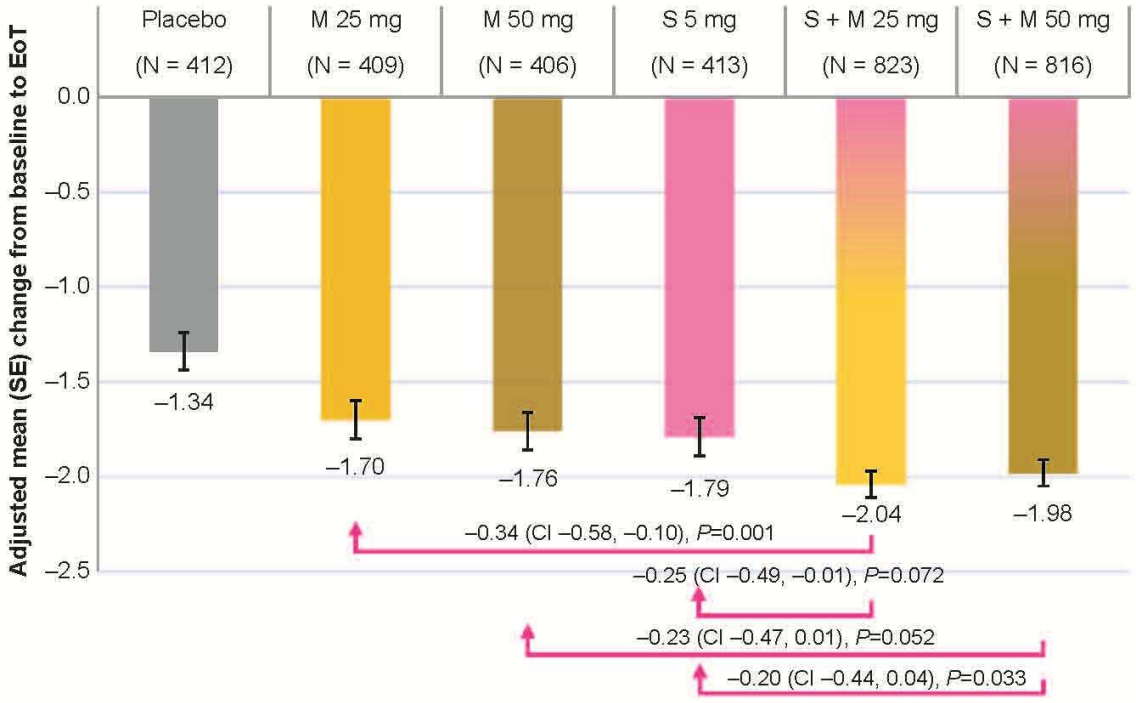


Figure 2B

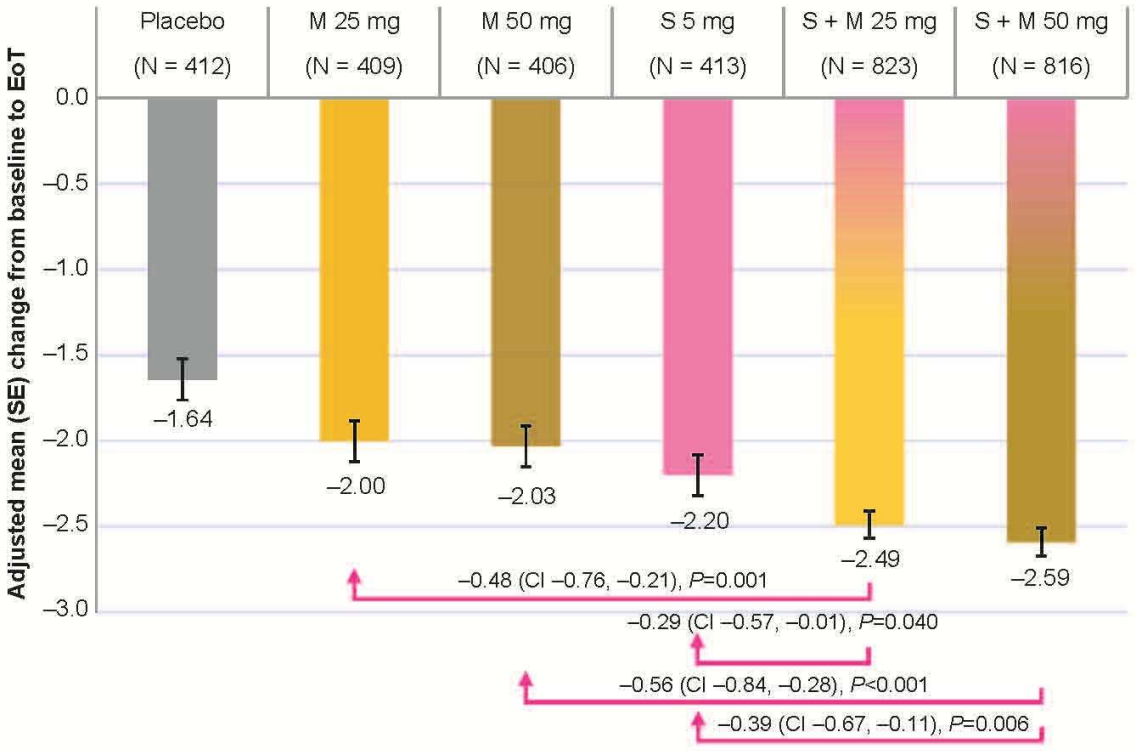


Figure 3A

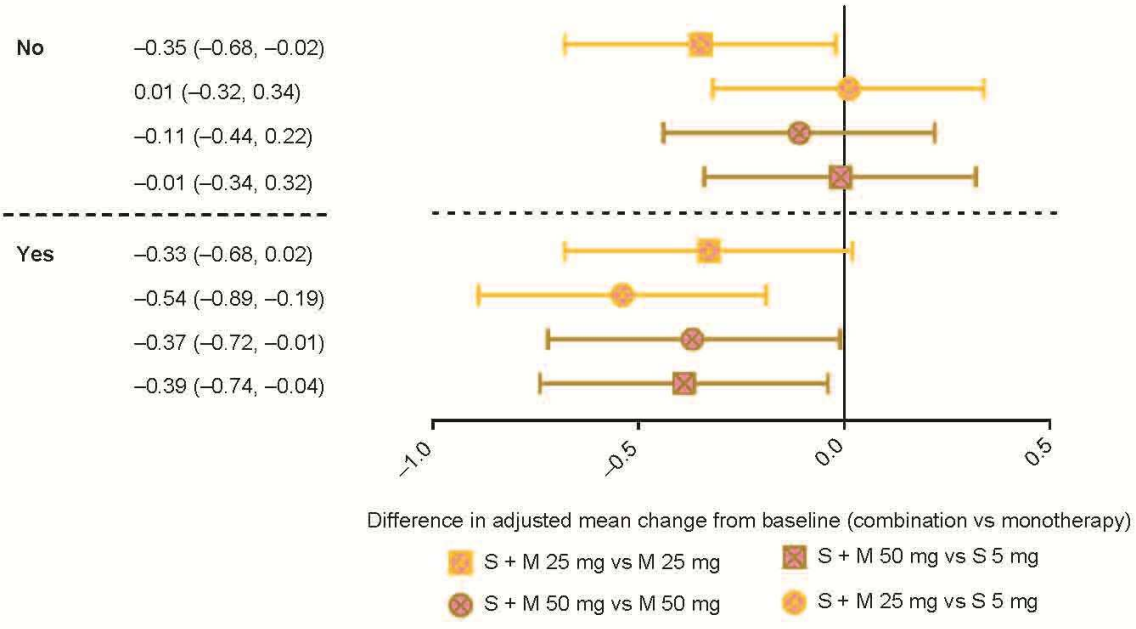


Figure 3B

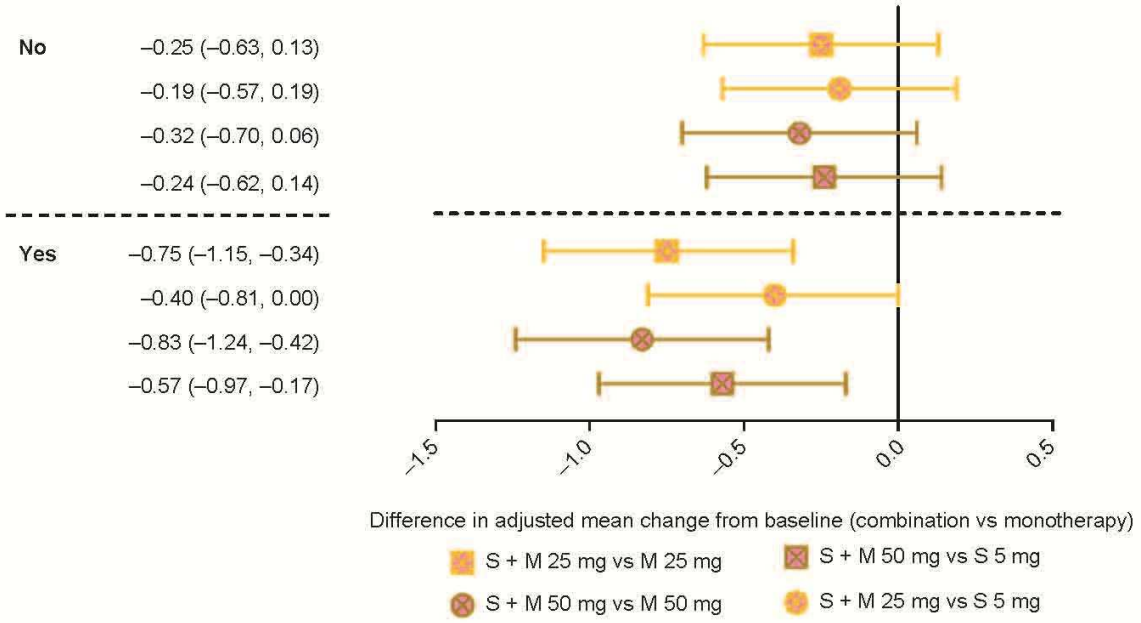
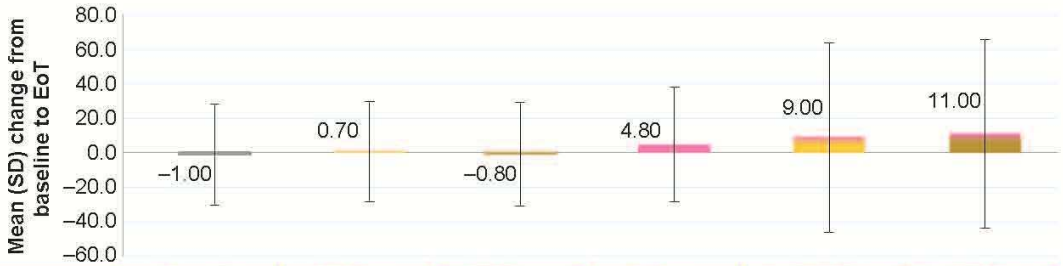


Figure 4



		Placebo (N = 429)	M 25 mg (N = 423)	M 50 mg (N = 422)	S 5 mg (N = 423)	S + M 25 mg (N = 853)	S + M 50 mg (N = 848)
BL	**n**	**423**	**418**	**417**	**422**	**848**	**840**
	Mean	21.3	20.0	22.5	21.1	21.3	21.4
	(SD)	30.6	27.4	32.1	29.0	29.3	29.5
EOT	**n**	**415**	**404**	**406**	**415**	**822**	**818**
	Mean	20.6	21.3	22.1	25.5	30.5	32.6
	(SD)	29.7	29.3	33.5	33.9	57.7	57.0
	95% CI	(17.8, 23.5)	(18.5, 24.2)	(18.8, 25.3)	(22.2, 28.8)	(26.6, 34.5)	(28.7, 36.5)
	Change from BL						
	n	**410**	**401**	**404**	**414**	**821**	**815**
	Mean	–1.0	0.7	–0.8	4.8	9.0	11.0
	(SD)	29.4	29.1	30.0	33.3	55.0	54.9